REMARKS

Claims 1 and 3 are pending in the instant application. Claims 1 and 3 have been rejected. Claim 1 has been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §112

Claims 1 and 3 have been rejected under 35 U.S.C. §112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims. Specifically, the Examiner suggests that while being enabled for a compound comprising a baculovirus expressed recombinant Fel dI wherein the baculovirus expressed recombinant Fel dI comprises a sFv humanized anti-CD64 monoclonal antibody H22 fused to Fel dI chain 1 and Fel dI chain 2 wherein chain 1 and chain 2 are linked in series by a glycine/serine linker encoded by SEQ ID NO:5 as shown in Figure 1 for diagnosis of cat allergy, the specification does not reasonably enable any compound as set for in claims 1 and 3 forth diagnosis and treatment of cat allergy. The Examiner suggests that there is insufficient guidance provided by the specification on the hybridization conditions using primers SEQ ID NO:1-4 for amplifying the nucleic acid sequences that encode the Fel dI chain 1 and chain 2 and that, as evidenced by Wallace *et al.* and Sambrook *et al.*, such specificity in hybridization is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable. Accordingly, the Examiner suggests that

undue experimentation would be required to practice the claimed invention.

Applicants respectfully traverse this rejection.

MPEP 2164.01 states the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. Denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrick GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

Applicants believe that the skilled artisan could readily produce the nucleic acid sequences encoding Fel dI chain 1 and chain 2 using the guidance provided by the specification and what is well-known in the art of non-degenerate PCR methodologies to synthesize compounds of Claims 1 and 3. The specification clearly indicates that the nucleic acid sequences encoding Fel dI chain 1 and chain 2 may be amplified using primers of SEQ ID NO:1-4 which are complementary to cDNA sequences encoding Fel dI chain 1 and chain 2 located on isolated and commercially available plasmids, pET11dΔHR chain-1 *Feld*I and pET11dΔHR chain-2 *Feld*I, respectively (Immunologic Pharmaceutical Corp., Waltham, MA) (see pages 3 and 4 of the specification). To clarify the nature of the specificity of the primers and templates, Applicants have amended claim 1 to recite that the primers used in the amplification of Fel dI chain 1 and chain 2 nucleic acid sequences are

complementary to said sequences which may be located on specific templates (see page 4, line 21 of the instant application). Thus, having a known template from which to amplify a predictably sized amplicon, known complementary primer sequences, and an art-established method for calculating an appropriate hybridization temperature (*e.g.*, 2-5°C below T_d wherein T_d=2°[number of A + T residues] + 4°[number of G + C residues]) in which two complementary strands will form a duplex (see Wallace *et al.* page 435-436), it would be reasonable to expect that one of skill, without undue experimentation, could amplify Fel dI chain 1 and chain 2 for production of the compounds of Claims 1 and 3. Withdrawal of this rejection is therefore respectfully requested.

Claims 1 and 3 further stand rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner suggests that the specification does not teach the specific PCR conditions using primers 1-4 to amplify any nucleic acid sequences that encoded Fel dI chain 1 and chain 2 and that claim 1 recites more than one nucleic acid sequence encoding chain 1 and chain 2 which are amplifiable by the specific set of primers. Thus, the Examiner suggests that given the indefinite number of undisclosed nucleic acid sequences and PCR conditions for making the claimed compound, the compounds of claim 1 and, based on dependency, claim 3, are not adequately described. Applicants respectfully traverse this rejection.

As indicated *supra,* Applicants have amended claim 1 to recite that primers of SEQ ID NO:1-4 are complementary to cDNA

sequences encoding Fel dI chain 1 and chain 2 located on commercially available plasmids, pET11dΔHR chain-1 *Feld*I and pET11dΔHR chain-2 *Feld*I. Further, Applicants have amended claim 1 to indicate that a single nucleic acid sequence encoding either chain 1 or chain 2 is amplified by PCR using the primers set forth in claim 1. Accordingly, given the specific combination of 5′ and 3′ sequences flanking chain 1 and chain 2 nucleic acid sequences, the specific template from which chain 1 and chain 2 nucleic acid sequences may be amplified, and what is well-known in the art regarding non-degenerate PCR amplification and appropriate conditions thereof, there is clearly adequate written description for making the claimed compounds of claim 1 and 3. Withdrawal of this rejection is therefore respectfully requested.

Claims 1 and 3 have also been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner suggests that the recitation of "nucleic acid sequences that are amplifiable by PCR" in claim 1 is indefinite and ambiguous. Applicants respectfully traverse this rejection.

As indicated *supra*, Applicants have amended claim 1 to clarify that a single nucleic acid sequence encoding either Fel dI chain 1 or chain 2 may be amplified by PCR from the commercially available plasmids pET11dΔHR chain-1 *Feld*I and pET11dΔHR chain-2 *Feld*I, respectively. Withdrawal of this rejection is therefore respectfully requested.

II. Rejection of Claims Under 35 U.S.C. §103

Claim 1 has been rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,547,669 in view of U.S. Patent No. 5,395,750.

U.S. Patent No. 5,547,669 teaches Fel dI chain 1, Fel dI chain 2 and Fel dI chains 1 and 2 linked together via a linker such as any non-epitope amino acid sequence or other appropriate linking or joining agent. The Examiner suggests that the claimed recombinant Fel dI as recited in claim 1 differs from the reference in that the recombinant protein is expressed in baculovirus, which has no patentable weight because a compound is a compound, and has a glycine/serine linker of SEQ ID NO:5.

U.S. Patent 5,395,750 teaches a method of making a compound such as synthetic single chain antibody sequence, for example, heavy and light region sequences of any antibody is linked by a glycine/serine linker that is identical to the claimed linker sequence of SEQ ID NO:5.

The Examiner suggests that it would have been obvious to one of ordinary skill in the art at the time that the invention was made to substitute the linker as taught by the '669 patent for the flexible linker taught by the '750 patent to generate a recombinant Fel dI molecule composed of chain 1 and chain 2 in series which has binding to IgE at a level comparable to that of natural Fel dI, *e.g.*, at a 1:100 dilution as indicated in Figure 14 and column 23, lines 61-62 of the '669 patent. The Examiner suggests that one of skill in the art would have been motivated to do this because the '669 patent teaches that recombinant Fel dI is useful for treating and diagnosing sensitivity in an individual to cat allergen such as Fel dI. The Examiner further

suggests that since the specification fails to identify the specific nucleic acid sequences encoding chain 1 and chain 2 of claim 1, the structure of the claimed compound appears to be the same as that of the reference compound, and therefore would obviously bind to human IgE and IgG at a level comparable to that of natural Fel dI as claimed. Applicants respectfully traverse this rejection.

At the onset, Applicants respectfully point out to the Examiner that the only mention of a flexible linker in the '669 patent is column 10, lines 62-67, wherein there is a mere suggestion of using a linker of any non-epitope amino acid sequence or other appropriate linking agent. There is no subsequent use or discussion of the nature of such a linker, *i.e.*, the length or sequence.

As set forth in amended claim 1, chain 1 is amplifiable by PCR from a template such as plasmid pET11dΔHR chain-1 *Feld*I using Fel dI chain 1 complementary primers of SEQ ID NO:1 and SEQ ID NO:2. These primers hybridize and amplify a nucleic acid sequence encoding the entirety of chain 1 of Fel dI, *i.e.*, corresponding to amino acid residues 1 to 70 of Figure 1 of the '669 patent. Further set forth in amended claim 1, chain 2 is amplifiable by PCR from a template such as plasmid pET11dΔHR chain-2 *Feld*I using Fel dI chain 2 complementary primers of SEQ ID NO:3 and SEQ ID NO:4. These primers hybridize and amplify a nucleic acid sequence encoding the entirety of chain 2 of Fel dI, *i.e.*, corresponding to amino acid residues 1 to 91 of Figure 2 of the '669 patent. Conversely, the '669 patent discloses recombining fragments X (corresponding to amino acid residues 7-33 of chain 1, Figure 1 of the '669 patent), Y (corresponding to

amino acid residues 29-55 of chain 1, Figure 1 of the '669 patent), and Z (corresponding to amino acid residues 14-39 of chain 2, Figure 2 of the '669 patent) to produce a recombinant Fel dI compound. Thus, the structure of the claimed compound is **not** the same as that of the reference compound, and therefore would not obviously bind to human IgE and IgG at a level comparable to that of natural Fel dI as claimed. Furthermore, it would not be obvious based on Figure 14, that any Fel dI recombinant would have the expected activity of binding to human IgE and IgG at a level comparable to that of natural Fel dI, even at a 1:100 dilution as suggested by the Examiner, as none of the recombinants (as represented by XYZ, XZY, YXZ, YZX, ZXY, and ZYX) approached the binding of natural TRFP. There was as much as a 2.5-fold difference in binding by even the best of the recombinants, *i.e.*, ZXY. It is respectfully pointed out that the particular reference to column 23, lines 61-62 of the '669 patent which was cited by the Examiner describes comparable binding levels to IgE of recombinant chain 1 or chain 2 alone, not of a recombinant X, Y, Z molecule. Furthermore, the '669 patent is silent as to the binding of a Fel dI recombinant to IgG.

MPEP § 2143 states that to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination must both

be found in the prior art, and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully disagree that it would be obvious to combine the teachings of the '669 and '750 patents to arrive at the claimed invention. As the '669 patent neither enables the use of, nor suggests the nature of, a flexible linker it would not be obvious to introduce a linker as taught by the '750 patent into a recombinant Fel dI of the '669 patent. Furthermore, there would be little reasonable expectation of successfully producing a recombinant Fel dI which binds to IgE or IgG at a level comparable to natural Fel dI based on the teachings of the '669 patent as only one of the recombinants taught by the '669 patent had any binding to IgE, and this recombinant lacked a flexible linker. Thus, introducing a flexible linker, as taught by the '750 patent, to a recombinant of the '669 patent would have an unpredictable influence on the binding of said recombinant to IgE. Moreover, neither reference, whether alone or combined teach or suggest all the claim limitations, *i.e.*, recombinant Fel dI binds human IgE and IgG at a level comparable to that of natural Fel dI. Thus, as the combined teachings of the '669 and '750 patent fail to establish a *prima facie* case of obviousness, withdrawal of this rejection is respectfully requested.

Claim 3 has been rejected as being unpatentable over U.S. Patent No. 5,547,669 in view of U.S. Patent No. 5,395,750 as applied to claim 1 and further in view of U.S. Patent No. 5,837,243.

The teachings of the '669 and '750 patents have been discussed *supra*.

U.S. Patent No. 5,837,243 teaches bispecific molecules such as cat allergen linked to humanized or single chain (sFv) antibody H22 that binds to CD64. This reference also teaches fusion molecules linked together via a linker such as glycine and serine.

The Examiner suggests that it would have been obvious to one of ordinary skill to link the single chain humanized antibody H22 of the '243 patent to Fel dI chain 1 and chain 2 in series as taught by the '669 patent using a linker such as glycine and serine as taught by the '750 patent. The Examiner further suggests that one having ordinary skill would have been motivated to do this because the '669 patent teaches recombinant Fel dI is useful for treating and diagnosing sensitivity in an individual to cat allergen such as Fel dI, the '750 patent teaches a flexible glycine serine linker, and the '243 patent teaches the antibody H22 is useful for targeting any antigen to the antigen presenting cell to a surface receptor such as CD64 on the antigen presenting cell thereby inducing tolerance to any antigen such as an allergen. Applicants respectfully traverse this rejection.

Applicants respectfully disagree with the suggestion that claim 3 is obvious in light of the teachings the '669 patent in view the '750 patent as applied to claim 1 and further in view of the '243 patent. As discussed *supra*, the combined teachings of the primary references fail to establish a *prima facie* case of obviousness by suggesting or motivating the skilled artisan to combine the teachings of the '669 and '750 patents to arrive at the instant inventive compound. As set forth by both the Court of Appeals for the Federal Circuit and the MPEP, when an independent claim is nonobvious under 35 U.S.C. § 103, then any claim

depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and MPEP § 2143.03. Accordingly, the cited combinations of prior art references can not render obvious the subject matter of claim 3. Withdrawal of these rejections is therefore respectfully requested.

Claim 1 has been further rejected as being unpatentable over U.S. Patent No. 5,547,669 in view of U.S. Patent No. 5,395,750 and Bei et al. (1995) *J. Immunological Methods* 186:245-255).

The teachings of the '669 and '750 patents have been discussed *supra*.

Bei et al. teach that the baculovirus system may be used to produce the single-chain antibody CC49 which reacts with pancarcinoma antigen, tumor associated glycoprotein, TAG-72. This reference further teaches a construct with sFv CC49 covalently joined to Fc(γ1) through a hinge and a construct having human IL-2 attached to the C-terminus of SCIg.

The Examiner suggests that it would have been obvious to one of skill in the art at the time the invention was made to substitute the *E. coli* expression vector as taught by the '669 patent for the *S. cerevisiae* vector or phage display vector as taught by the '750 patent for producing a compound comprising a recombinant Fel dI composed of chain 1 and chain 2 expressed in series and linked together by a glycine/serine linker of SEQ ID NO:5 as taught by the '669 patent, the '750 patent and Bei *et al.* The Examiner further suggests that one of skill in the art would have been motivated to do this because Bei *et al.* teach the salient features of baculovirus expression system including high efficiency of expression, ease of purification, time saving and

cost-effective method of scaling up production of functional proteins. Applicants respectfully traverse this rejection.

As discussed *supra*, the combined teachings of the primary references fail to establish a *prima facie* case of obviousness. The teachings of Bei *et al.* do not make up for the insufficient teachings of the primary references by suggesting or motivating one of skill in the art to introduce a flexible linker of the '750 patent into a recombinant Fel dI molecule, as taught by the '669 patent, such that there would be a reasonable expectation of successfully producing a recombinant Fel dI which binds to IgE or IgG at a level comparable to natural Fel dI. Thus, withdrawal of this rejection is respectfully requested.

III. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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